This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 3:
A61K 9/00; A61M 37/00

A1

(11) International Publication Number: WO 81/01515

(43) International Publication Date: 11 June 1981 (11.06.81)

(21) International Application Number: PCT/SE80/00315

(22) International Filing Date: 4 December 1980 (04.12.80)

(31) Priority Application Number: 7910018-6

(32) Priority Date: 5 December 1979 (05.12.79)

(33) Priority Country: SE

(71) Applicant *(for all designated States except US)*: AB MEDLINE [SE/SE]; Wallingatan 37, S-111 24 Stockholm (SE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: BRUNDIN, Jan-Olof [SE/SE]; Skyttevägen 21, S-181 46 Lidingö (SE).

(74) Agents: HAGELBERG, Torvald et al.; Patentbyrån West-Patent, Stora Nygatan 15, S-411 08 Göteborg (SE).

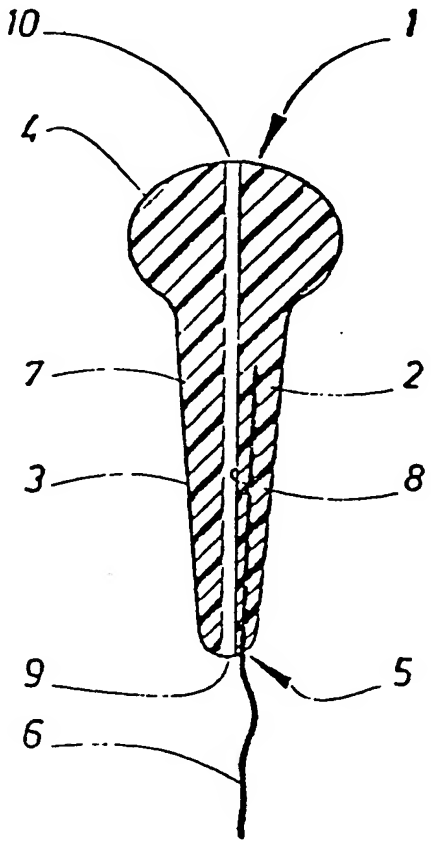
(81) Designated States: AT, AT (European patent), AU, BR, CH, CH (European patent), DE, DE (Utility model), DE (European patent), DK, FI, FR (European patent), GB, GB (European patent), HU, JP, NL, NL (European patent), NO, RO, SE, SE (European patent), SU, US.

Published
With international search report
In English translation (filed in Swedish)

(54) Title: ADMINISTRATION OF MEDICAL ACTIVE SUBSTANCES

(57) Abstract

Means for the supply of medical active substances and exhibiting a body (2) which is provided with the medical active substance being such that it is possible to be absorbed by the body tissues when the substance by means of the body is brought in contact with the same. The body (2) is substantially elongated in form and provided to be introduced in a body channel. The material in the body is a hydrogel which in contact with a fluid producing body tissue will absorb the body fluid and thereby will swell in volume whereby it being anchored in the channel and pressed against its walls. As a result the medical active substance during a period of time will be transferred to the surrounding tissues.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria
AU	Australia
BR	Brazil
CF	Central African Republic
CG	Congo
CH	Switzerland
CM	Cameroon
DE	Germany, Federal Republic of
DK	Denmark
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
HU	Hungary
JP	Japan
KP	Democratic People's Republic of Korea
LI	Liechtenstein
LU	Luxembourg
MC	Monaco
MG	Madagascar
MW	Malawi
NL	Netherlands
NO	Norway
RO	Romania
SE	Sweden
SN	Senegal
SU	Soviet Union
TD	Chad
TG	Togo
US	United States of America

Title:
Administration of medical active substances

Technical field:

The present invention relates to means for administrating of medical active substances locally to certain parts of the body in human beings or animals.

Background:

In order to obtain certain medical effects it can in certain cases be advantageous or necessary that some substances are brought in contact with a body tissue for a longer period of time to be absorbed in a slow sequence and thereby affect a human body or an animal body locally or more in general. As an example of a simple type of such a treatement, a dermatologic treatement can be mentioned, by applying of an ointment for example, which will remain for a longer period of time and from which the skin can absorb certain active substances. As another example can be mentioned that for prophylactic or therapeutic reasons contact linses are impregnated with the soft type of a remedy, as some kind of antibiotics, which, while the contact linse is in place can be absorbed by the eye.

Technical problem:

The two mentioned known cases have been connected to external treatement. For internal treatement certain difficulties are present when using these methods. An application of the medical active substance can thus not be used in local treatement of body channels covered with mocous membrane, at least not when it necessitates a longer action, as the substance will be rinsed away by the body fluids which will moisture the mocous membrane. Nor can the other mentioned known method with a carrying member for the medical active substance on the spot of treatement be used. It is difficult to have a carrying member remaining against the surface of the body channel, particularly in connection with body movements and when body fluids is passing the channel at the same time as the control of the position of the carrying member is difficult to establish in connection with internal treatement.

Solution:

The mentioned problem of the invention is solved by using a body of hydrogel as a carrier for the medical active substance, which swells when absorbing body fluid. By a suitable dimensioning and swelling factor of the body it can fill the body channel and remain in the same by means of a pressure against its walls. Hereby the active substance which is absorbed in the body can be made to act upon the walls of the channel during a longer period of time without any risk that the carrying member will be displaced or rinsed away.

In order to carry out the invention two special cases are suggested, whereby also specific medical substances are stated, which can establish a favourable medical effect at the application in question.

Advantages:

By means of the invention the advantage is obtained that an internal local treatement can be established even when longer time of influence is necessary for the medical active substance. Particular advantages are obtained in connection with the stated cases of treatement by using the mentioned substances.

Brief description of drawings:

In the accompanying drawings Fig. 1 shows the device in applied condition in a first embodiment; Figs. 2-4 show in longitudinal sections three different embodiments of the device, intended for the first applied condition; Fig. 5 shows the device in applied condition in a second embodiment; and Figs. 6, 7 show a longitudinal and cross section of an embodiment of the device intended for the second applied condition.

Best mode of carrying out the invention:

The means according to the invention is in the form of a material, which, when it is brought into contact with a body fluid, swells up volumetrically by at least 20% measured as linear expansion. The body is substantially inert to the body fluids and surrounding tissues apart from its swelling property. The swelling of the body in contact with a body fluid is preferably at least 40 % by way of ex-

BUREAU OMPI WIPO

ample at least 80%. The swelling can vary between 20 - 300 % linear measurement. The body is intended to be inserted into body channels in human beings and animals according to the examples in the cervix channel and in the oviduct.

As the material in the body is hydrophilic, it can be made to absorb water soluble or emulsifiable substances, and the idea of the invention is to arrange the body so that its hydrophilic material contains active substances. As the body is well suited to be introduced into and remain in body cavities on account of its swelling property, whereby the body due to suitable dimensioning in size and swelling capacity can be brought to establish a good contact with the walls of the body cavity, it is also well adapted in such connections to serve as carrier of body active substances, which can suitably be administered locally by letting the substance in question during a certain period of time remain in contact with the body tissue. The body tissue is in this case thus the walls of the cavity, i.e. a mucous membrane.

As example of two important fields of application which shall be illustrated later it can be mentioned the provocation of an abortion by means of introducing a body with the mentioned properties through the cervix channel and into the uterus. As the body is inserted in its non-swollen condition, it can be of small dimensions and thereby be easily introduced, while after absorbing water from the body fluid it swells up and expands the cervix. By this arrangement the expulsion of the foetus, initiated by an abortion being directly administered to the uterus, is facilitated. The active substance can be prostaglandines, or analogous substances which, after having acted for a certain time, produce an abortive effect. By this arrangement a particularly effective abortion method is obtained, which involves small risks of damage to the exposed organs. To this can be added that the active substance is brought directly to the spot that shall be treated and that a local effective dose can be administered without the human or animal body being exposed to any general effect of consideration. If one instead would administer prostaglandines in the form of a general dose, by way of exemple by means of an injection, it must be administered in such a high dose in order to produce the desired effect that one would experience a general effect in the form of vomitting, nausea and attacks of diarrhoea.

BUREAU

In the second embodiment, which is illustrated in the following, is stated a sterilizing by occlusion of the oviducts. It is known that certain substances, namely cytotoxic sclerosic substances at a relatively long contact with body tissues can initiate the forming of connective tissues. This effect can be utilized for blocking of the oviducts for the purpose of sterilizing. It is, however, necessary that the substance in question will be in contact with the mocous membrane for a longer period of time, which is difficult to establish in connection with conventional methods, like wetting or inserting a quantity of ointment containing the substance. According to the invention it is suggested that the substance in question be brought to be absorbed in a body of the mentioned swellable kind, which will be inserted in the oviduct and remain there so that the mentioned forming of connective tissues will be initiated. Before the connective tissue has been formed and occluded the oviduct, the body, which is anchored by its swelling and thereby occludes the oviduct, serves as a hindrance for the ovum to pass whereby a temporary preventive effect occurs.

The means according to the invention is moreover advantageous according to the pharmaceutical treatement because of the fact that the swelled-up body in its resilient condition provides a very good contact with the surrounding body tissues, whereby a very good and well adjustable transmission of the active substance can take place. The soft body is moreover compatible with body tissues and can remain for a long period of time without producing any irritation. It can be adapted whithin wide limits to a desired duration of its giving off the active substances as well as to the size of the dose. Besides, as mentioned previsously, expanding and occlusion respectively is obtained.

The geometrical shape of the body, which is introduced into the cervix is not so critical, and the body for example can be of substantially cylindrical, spherical, egg-shaped or of hour-glass form. Its cross-section and design in other respects shall after the swelling-up has taken place be adapted to the intended cross-section and shape of the channel-shaped cavity. The cross-section of the not-swollen body is so adapted to the cross-section of the channel that the body can be introduced into the cavity with play or under

BUREAU OMPI WIPO

a slight widening of its walls so that the introducing can be made with the least possible difficulty. A thread is suitably attached to the body in order to facilitate its extraction without any operative measure. This thread can be of radiopaque material, so that a control of the position of the body can be made. The body itself can alternatively be of radiopaque material.

As mentioned the material of the body swells up in contact with the body fluid by at least 40 %, suitably at least 80 %, and it can even swell as much as 300 % or more. The material shall otherwise essentially be inert to the body fluid and neither be harmful to the body tissues nor be absorbed by them. Hydrogels are a suitable group of material. These materials swell up by absorption of water out of the body fluid. Polymers and copolymers of the acrylic type are suitable hydrogels, as for example cross-linked polyacrylamide and polymers and copolymers of esters of metacrylic acid with at least one hydroxy-group in the lateral chain. 2-hydroxy-ethyl-metacrylate is a suitable monomer, in which the ester-group can be derived from diethyleneglycol or triethyleneglycol. 2,3-dihydroxypropyl-metacrylate is for example also useful. Polyfunctional acrylates as diesters or corresponding glycols, by way of example ethylene-glycol-bis-metacrylate are useful as cross-linking agents.

A copolymer of a hydrophilic monomer and a hydrophobic monomer is another example of material suitable for the body according to the invention. The water absorbing property and by that the swelling-up can be varied within wide limits by means of a variation of the proportions between the hydrophilic and the hydrophobic monomer of this material. Monomers within the group comprising N-vinyl-pyrrolidones and vinyl-pyridines can be mentioned as examples of the hydrophilic component, and monomers of the group comprising metacrylates and methylmetacrylates can be mentioned as examples of the hydrophobic component. A polymerisation does suitably take place by subjecting the starting material to electromagnetic radiation within the ultraviolet-gamma radiation range or by heating. A sterilization of the body is then also obtained, which is important in the present connection in order to avoid the risk of microbial organisms being brought into the body tissue. This is important, as the means is intended for use in internal body cavities susceptible to infections.

BUREAU OMPI WIPO INTERNATIONAL

The incorporation of the active substance into the material of the body can take place by said material after the polymerisation being placed in a sterile solution or possibly in an emulsion of the active substance or substances in water. The hydrophilic material of the body will then absorb the water solution or the emulsion respectively. If one lets off the water afterwards by evaporation, the active substance remains in the material of the body, and it can subsequently be dissolved, when the body again is brought into contact with a fluid with abundant contents of water, thus, the body fluid after the body has been introduced. The body can be impregnated with the active substance to different depths by a control of the concentration of the fluid and the duration of the fluid absorption, which leads to different duration of the treatment, thus, the absorption by the body of the active substance, as well as the dosage. It is even possible to carry out the impregnation in several steps in order to obtain a gradually varying concentration and possibly varying kind of substance, whereby a treatment, which can be varied with respect to time, can be attained.

The body should essentially be resilient and only to a very limited extent be plastic deformable. In non-swollen (non hydrated) condition it may be stiff and/or hard, but in connection with the swelling it should suitably get softer. The body may contain compounds that make it more radiopaque, by way of example salts of barium or bismuth or metallic powder (for example silver).

Thus, the body in its introduced position obtains a good anchoring in the body channel or the cavity, where it is introduced after the material of the body has absorbed body fluid and swelled up. However, this takes some time, and before the swelled-up condition has been reached, the body exhibits a play relative to the surrounding walls of the tissue. As mentioned the body is so adapted in dimension to the channel that it can easily be introduced in said cavity.

This means that the body not always will obtain a secure anchoring until the swelling-up has taken place, and it can therefore ensue a period of uncertainty immediately after the insertion, when the body under unfavourable circumstances can displace itself due to the flow of body fluid through the channel or movements of the

BUREAU OMPI WIPO INTERNATIONAL

carrier of the inserted body. The body may however be provided with at least one means of a material of adapted stiffness. This means exhibits outer portions, which at least in the non-swollen condition of the body project outside of the body and so far that they will arrive in contact with the walls surrounding the cavity, when the insertion of the body has taken place in the desired manner. By this arrangement these projection portions act as blocking means, which under spring action keep the body in its inserted place. These springing portions are suitably made with "ratchet" locking property, so that they springingly yield in the direction of insertion, but tend to expand in connection with a movement out of the channel.

Thus, the projecting portions of the means serve the purpose of anchoring means only or substantially before the body has acquired its swollen condition. They can therefore be of such dimension that for the most part they will be inside the surface of the body, when the same has acquired its swollen condition and thereby is held well in place. By this arrangement one avoids that the projecting portions in too high a degree are pressed in into the surrounding body tissue during the duration of the application of the means, when the body has acquired its swollen condition, and not either in connection with the extraction.

A means 1 according to the invention and of a preferred embodiment intended for insertion into the cervix channel of a woman is shown in Figs. 1-4. It is formed as a body 2 of long extension made of the swelling material and exhibiting a thin end 3 and a mid-portion 7 and an outer bulb-shaped end 4. A thread 5 preferably made of polyamide fibre is incorporated into the body 2 and terminates inside the end 3, but extends outside of the body at the end 4 with a free portion 6. It should be radiopaque. A draining duct 8 with openings 9 and 10 may extend through the body.

As an example of suitable dimension of the body 2 in connection with the intended application can be mentioned a length of the body in the unswollen state of 70 mm apart of the free portion of the thread 6 and a greatest diameter of 4 mm at the end 4 and 12 mm at the midportion 7.

A variant of the means for insertion in the cervix channel and the uterus is shown in Fig. 4. If with respect to the means of the

BUREAU OMPI WIPO

form illustrated in Fig. 3 it can be said that it is of mushroom-like shape, the means according to Fig. 4 exhibits a rather hour-glass shape, both its ends thus being expanded and the mid-portion made as a narrower waist.

One or several means 11 for said anchoring of the body, which in this embodiment is of cylindrical shape, is illustrated in Fig. 5. The means extends through the same and in the non-swollen condition of the same exhibits projecting portions 12. The mid-portion, from which the outer portions 12 depart, is located inside the material of the body 2 in its non-swollen condition and thus forms an anchoring device for the means 11. The thread 5 moreover extends through a hole 13 of the means, whereby a mutual extraordinarily effective anchoring of the means and of the thread 5 in the material of the body 2 is obtained.

A body 31 according to the invention intended to be inserted in a woman's oviduct is shown in longitudinal section in Figs. 6 and 7. It consists of a prolonged cylindric (compare Fig. 7) body 32 of the mentioned swellable material with an inner rounded end 33 and an outer ball-shaped edge 34. In the body 32 is inserted a thread 35 which terminates inside the inner edge 33 but stretches out of the body close to the edge 34 with a free portion 36.

The thread 35 is preferably of polyamide fibres, at least partly opaque for X-rays or the body can be provided with an opaque reinforced element.

Even in this case the body has the function as a carrier of a medical active substance. It has as a purpose to initiate a forming of connective tissue in the oviduct so that the same will be occluded. For this a substance is required to initiate the body to form connective tissue. For this purpose certain cytotoxins are available. Among such cytotoxic sclerosic substances quinacrine-hydrocloride and ethanolformalin can be mentioned. Particularly quinacrine-hydrocloride has a specific effect on the mocous membrane of the oviducts, so that this will be initiated to form connective tissue which leads to a remaining non reversible occlusion of the oviducts. In order to establish this effect, however, an influence of the substance during a considerable long time as a couple of weeks is required. This can be provided by the carrier being inserted in the oviduct and an-

BUREAU OMPI WIPO

chored there by its swelling so that it remains long enough for forming of the connective tissue.

Even in this case of application the body can be provided with the mentioned anchoring means, shown in Fig. 4.

The means 1 according to Fig. 3 inserted in the cervix of a woman is illustrated in Fig. 1. The womb cavity is indicated with 20 and the cervix or neck of the uterus with 24. As is evident from the figure the knob-shaped expanded portion 4 of the means is in the cavity of the uterus whereas the rest of the means extends through the cervix channel. After the body has been inserted, it absorbs water from the body fluid and swells up. It then fills up the cervix channel and expands the same. By contact with the surrounding body tissues the latter ones absorb the active substance carried by the material of the body, in this case thus prostaglandines or analogous substances, which after some time of action produce an abortive effect. Fluid formed but not absorbed by the material of the body can escape through the drainage duct 8. As is evident from the figure, the thread 5 extends out through the uterine entrance 21, whereby an indication is obtained that the means remains in place and a possibility is provided to pull out the body, when the treatment shall be discontinued. It is of course within the scope of the invention that a means of similar kind as the means 1 can be used for treatment of inflammatory conditions in the uterus. The body shall in such a case be carrier of for example some kind of antibiotics.

In Fig. 5 is shown how the device 31 is inserted in the oviducts 37 of a woman. To the right is shown how immediately after the insertion, the body 31 still keeps its prolonged thin shape whereby it is easy to insert in the oviduct 37. To the left is shown how the body after having been in contact with the body tissues for a time has swollen by absorbing body fluids, whereby it completely occludes the channel and obtains a good anchoring to the same. The free portion 36 of the thread 35 extends downwards to the uterus 38 and makes it possible to remove the device in a simple way and also to control that the same remains in place.

After insertion the body 31 encloses the oviduct 37 so that a preventive effect arises, and an ovum cannot pass down through

BUREAU OMPI WIPO INTERNATIONAL

the same, nor can sperms pass upp through the same. After a period of time the previously described substance initiates a forming of connective tissue in the oviduct which finally occludes the same. After this has taken place the body 31 is not necessary. It can however remain as it has no damaging effect. If it should be discharged after that the connective tissue is formed, the fertility is not effected.

In the foregoing some examples have shown how the device can be designed and how it can be used. Except from this other designs and other forms of application can be imagined within the scope of the invention as stated. The different elements of the device like different form-elements, the pull out thread and the anchoring means do not need to be bound to each other in the way that has been stated but can be combined even in other ways.

BUREAU OMPI WIPO INTERNATIONAL

Claims:

1. Means for administration of active medical substances and comprising a body (2; 31) which is provided with the medical active substance and provided to be in a position resting against the body tissue in a human being or an animal, whereby the medical active substance is of such a kind that it can be absorbed by the body tissue when the substance by means of the body is brought in and remains in contact with the body tissue during a period of time, CHARACTERIZED BY that the body (2; 31) preferably being elongated in shape and provided to be inserted into a body channel (24; 37), that the material in the body is a hydrogel which in contact with fluid producing body tissues absorbs body fluid and thereby swells volumetrically at least 40% measured as linear expansion and that the body to its cross-section dimension in unswelled condition is provided to be inserted into the body channel and in swelled condition to widening itself to a dimension exceeding the normal cross-section of the body channel so that the body after the insertion is anchored in the channel and pressed against its walls and a transmission of the medical active substance to the body tissues surrounding the body will occur.

2. Means according to claim 1, CHARACTERIZED BY to the body (2; 31) is attached an indicator- and extraction thread (5; 35) which with a free end portion (6; 36) is extending outside of the body (2; 31).

3. Means according to claim 1 or 2, CHARACTERIZED BY in the body (2) is included ratched means (12) with outer end portions which are provided to bend by the moving of the body in the direction of insertion into the body channel (24; 37) but to extend out of the body by attempts to move the body against the direction of insertion, which means (12) are so arranged in the body (2) that end portions of the means are extending out of the body a relatively long distance in the unswelled condition of the body but by extending a short distance or are in a position entirely inside the surface of the body in the swelled condition of the same.

4. Means according to any of the preceding claims, CHARACTERIZED BY the hydrogel in the body (2; 31) comprises a copolymer of a hydrophilic monomer and a hydrophobic monomer whereby the

BUREAU OMPI WIPO INTERNATIONAL

swelling property of the body being adjusted by the proportions between the two monomers.

5. Means according to any of the preceding claims, CHARACTERIZED BY the body (2) to its dimension is provided to at least partly be contained in the cervix channel and that the medical active substance is an abortive active substance as prostaglandines or an analogous substance.

6. Means according to claim 5, CHARACTERIZED BY the body (2) at its middle portion exhibiting a cylindrical or slight conical first portion (3, 7) and at least at the one end a wider, bulb-shaped end portion (4) whereby the first portion is provided to rest in the cervix channel while the second portion, the end portion or portions respectively are provided to be positioned in connection to the end or the ends of the cervix channel.

7. Means according to any of the claims 1-4, CHARACTERIZED BY the body (31) to its dimension is provided to be contained in the oviduct (37) of a woman or an animal and that the medical active substance is a sclerosic substance of cytotoxic type as quinacrine-hydrochloride or ethanolformalin.

BUREAU OMPI WIPO

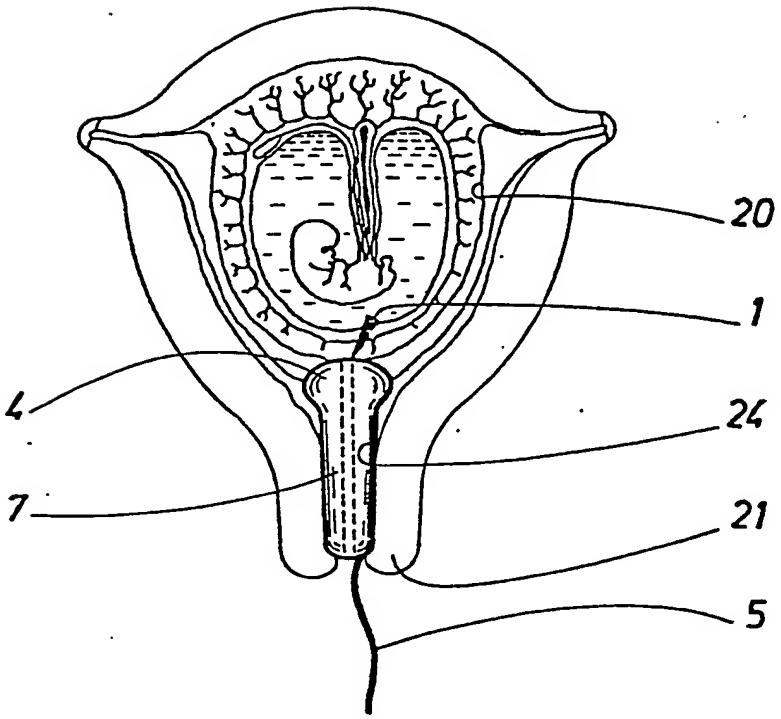


FIG.1

BUREAU OMPI WIPO

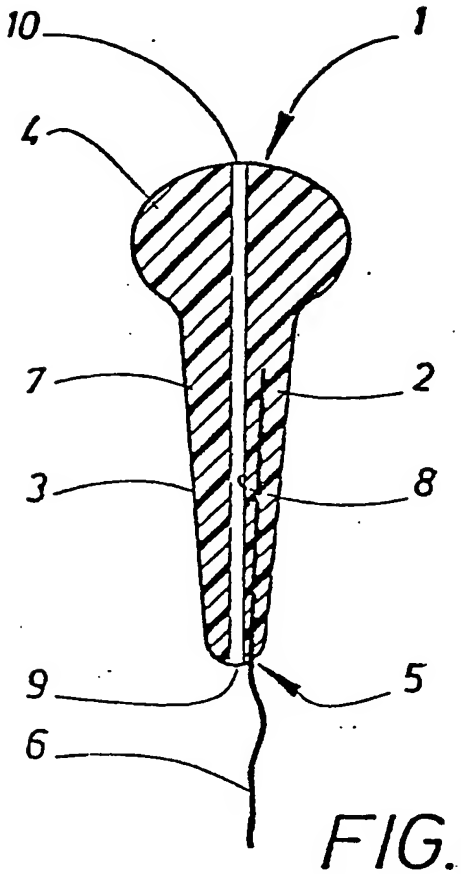


FIG.2

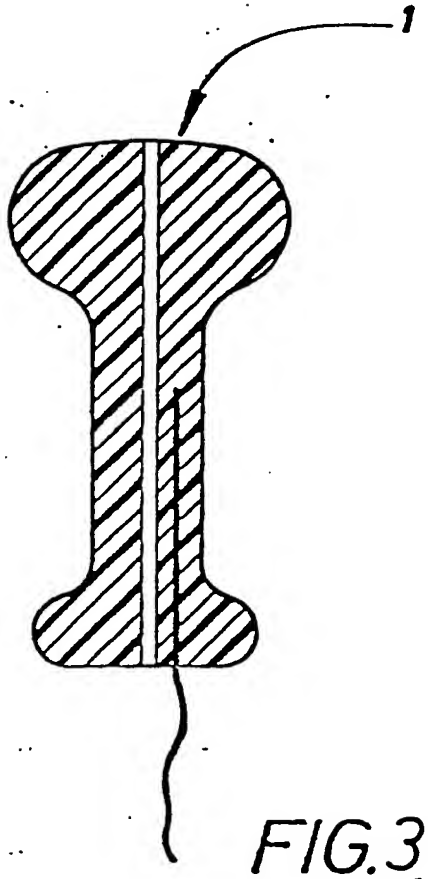


FIG.3

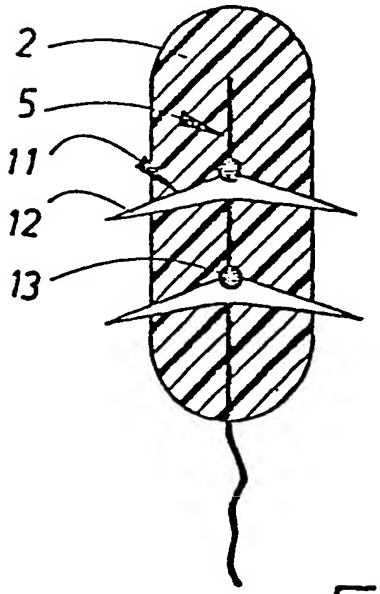


FIG.4

BUREAU OMPI WIPO INTERNATIONAL

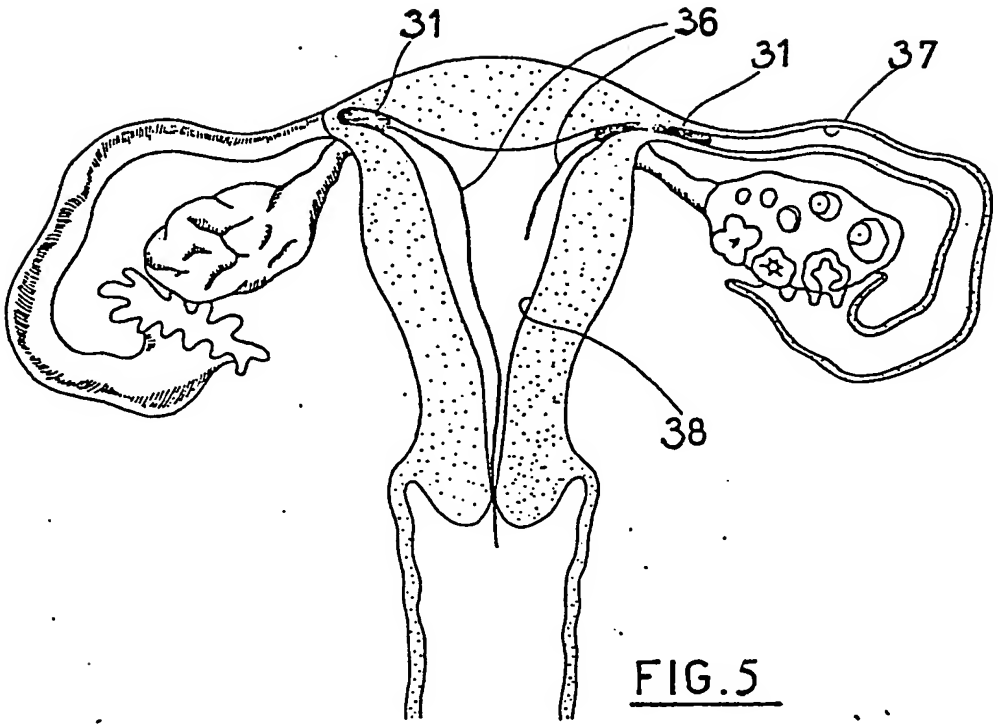


FIG.5

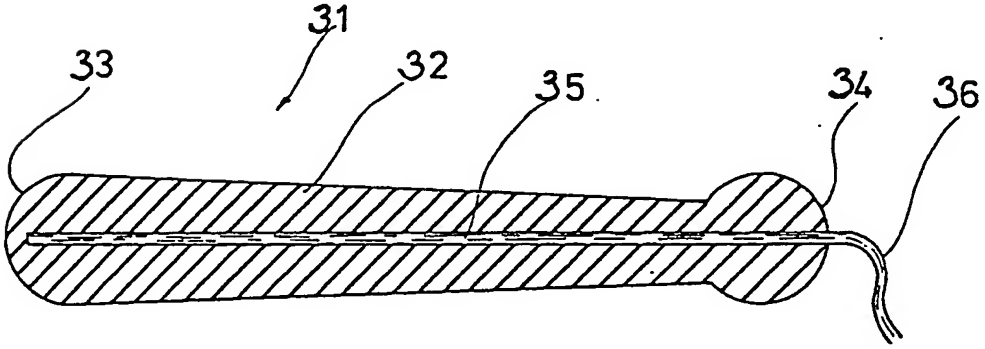


FIG.6

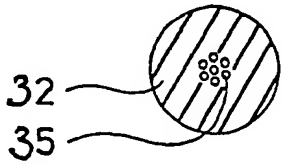


FIG.7

BUREAU OMPI WIPO INTERNATIONAL

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE80/00315

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC 3

A 61 K 9/00, A 61 K 37/00

II. FIELDS SEARCHED

Minimum Documentation Searched 4

Classification System	Classification Symbols
IPC 3	A 61 K 9/00, A 61 K 37/00, A 61 F 13/20
National Cl	30h:9/02
US Cl	117:72; 260:2.5; 424:21; 424:27

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched 5

SE, NO, DK, FI classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT 14

Category *	Citation of Document, 16 with indication, where appropriate, of the relevant passages 17	Relevant to Claim No. 18
X	SE, A, Patent application 7603618-0 published 1978, January 30, AB Fedline	1-7
X	US, A, 3 220 960 published 1965, November 30, Otto Wichterle and Dragoslav Lim	1-7
X	US, A, 3 551 556 published 1970, December 29, Karel Climent, Jiri Vacik, Zdenek Ott, Wladimir Stoy, Miroslav Stol and Otto Wichterle	1-7
A	US, A, 3 674 901 published 1972, July 4, Thomas H. Shepherd, Francis E. Gould	1-7
A	US, A, 3 695 921 published 1972, October 3, Thomas H. Shepherd and Francis E. Gould	1-7

* Special categories of cited documents: 15

"A" document defining the general state of the art

"E" earlier document but published on or after the international filing date

"L" document cited for special reason other than those referred to in the other categories

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but on or after the priority date claimed

"T" later document published on or after the international filing date or priority date and not in conflict with the application, but cited to understand the principle or theory underlying the invention

"X" document of particular relevance

IV. CERTIFICATION

Date of the Actual Completion of the International Search 3	Date of Mailing of this International Search Report 3
1981-02-09	1981 -02- 12
International Searching Authority 1	**Signature of Authorized Officer 20**
Swedish Patent Office	Gerth Gierer